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DRUG DISCOVERY

Proteins as the molecular markers of male fertility

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Proteins play a key role in many functions such as metabolic activity, differentiation, as cargos and cell fate regulators. It is necessary to know about the markers involved in male fertility in order to develop remedies for the treatment of male infertility. But, the role of the proteins is not limited to particular function in the biological systems. Some of the proteins act as ion channels such as catsper and proteins like Nanos acts as a translational repressor in germ cells and expressed in prenatal period whose role in male fertility is uncertain. Rbm5 is a pre mRNA splicing factor necessary for sperm differentiation whose loss of function results deficit in sperm production. DEFB114 is a beta defensin family protein necessary for sperm motility in LPS challenged mice where as TEX 101 is a plasma membrane specific germ cell protein whose function is not clearly known u to now. Gpr56 is another adhesion protein whose null mutation leads to arrest of production of pups in rats. Amyloid precursor protein role in Alzheimer's disease is already known but it plays an important role in male fertility also but its function is uncertain and has to be considered while targeting APP during the treatment of Alzheimer's disease. The study on amyloid precursor protein in male fertility is a novel thing but requires further study in correlation to alzheimer's disease.

INTRODUCTION

Nanos is a highly conserved gene in D.melanogaster and acts as a RNA binding protein (1-7). It plays several roles in drosophila but the role of it in fertility in humans has yet to be studied. Three types of Nanos gene such as Nanos 1, Nanos2 and Nanos3 (8) are majorly studied and in which Nanos 3 involves in migration of primordial germ cells to gonads (7) and its presence in spermatogonia is necessary for differentiation during spermatogenesis.

Some of the proteins like ser/thr protein phosphatases and kinases are well known for regulating metabolism by phosphorylation and dephosphorylation events but their role in male fertility was not well known. However, the Protein phosphatase 4 is one of the ser/ thr phosphatases found to be necessary for preventing errors in the genetic exchange. It plays key role in maintenance of synaptonemal complex and generation of programmed ds breaks which is necessary for cross over events (9). Ser/thr protein kinase causes phosphorylation of H1, H2, H2AX and H3 (10) and is required for chromatin remodelling in mitosis and meiosis. It also plays a role in DNA compaction also.

Ion channel proteins like catsper an anion transporter known for maintaining the ion fluxes in the cells and also involves in maintenance of membrane potential and ion balance inside the cell and required for maintaining sperm motility through ca^{2+} ion fluxes. It plays an important role in male fertility through regulating sperm motility. Slc26 is an anion transporter necessary for transport of monovalent and divalent anions like chloride (Cl-), sulphate (SO42-), iodide (I-) and bicarbonate (HCO3-) (11) and also involved in differentiation in mouse.

Proteins that counteract oxidative stress in seminal plasma include SOD, catalase and GPx where as non enzyme antioxidants like α-tocopherol, urate (12-15), naphthoquinone and HCO_3^- were previously known for protection against oxidative stress but now these are well known for their role in sperm functional parameters also.

Another protein GPR 56 was one of the adhesion G- protein coupled receptor that functions in cell adhesion through G- protein coupled signalling (16). First report of its involvement in male fertility was known through testis cord remodelling by Guangchun Chen et al., (2010).

DYNLT1 is a 14 Kda protein occupying the L1 inner arm of cytoplasmic and flagellar dynein components (17, 18). It is also present in oocytes, sperm tails (19, 20) and Golgi complexes (21). It also functions in as dynein independent manner and is a cell fate regulator in neural progenitor cells (22).

There are many proteins that play a role in male fertility but this review is concise up to some of the major key proteins involved in male fertility.

Proteins involved in male fertility through phosphorylation and dephosphorylation events

Serine /threonine protein phosphatase PP4 homolog PPH 4 was normally found in budding yeast and its presence in C.elegans and D.melanogaster is proved to be necessary for DNA ds break formation initiation and cross over along with synapsis independent pairing and prevention of non homologous pairing in autosomes during the synapsis. But it doesn't prevent the synapsis dependent pairing of homologous chromosomes. The homology of these proteins is about 92% at aminoacid level in humans to that of mouse. The protein is necessary for formation of chiasma, thus recombination without affecting the loading of recombinant proteins Rad 51. Ds break forming capability with respect to phosphatase enzyme is an age dependent factor and found to be involved in the meiosis, and in division that occur in germ cells (9).

PP4 is necessary for the conversion of foci in to cross over through COSA-1 (Aya Sato-Carlton et al., (2014) and dephosphorylates SUN protein which is required for synapsis independent pairing (9) in the yeast.

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SSTK is a small protein kinase found on chromosome 8 and distributed with high similarity in mammals and is expressed in almost all the tissues. Phylogenetic analysis showed moderate similarity of SSTK to the testis specific ser/thr kinases TSSK1, TSSK2 and TSSK3, MAP kinase/microtubule affinity-regulating kinases MARK and MARK4, and the ELKL motif kinase EMK1 (10).

This protein consists of N and C lobes of a protein kinase domain containing catalytic and ATP binding domains in which catalytic residues include K41, E60, D135, N140, D154, and T170, a glycine rich motif in phosphate binding loop and the conserved sequence DFG in the active site. SSTK consists of tyr phosphorylation domains which are similar to phosphorylation inhibitory domains of cyclin dependent kinases Cdc2 and Cdk2 and TTY sequence similar to T- X-Y phosphorylation motif found in the activation loop of MAP kinase (10).

SSTK even though associate with HSP90-1, HSP70, and HSP70-1 doesn't phosphorylate them but necessary for proper maintenance of structure of sperm head, sperm motility and DNA condensation in sperm head as it phosphorylates H1, H2A, H2AX and H3 but not the H2B, H4 and TP1(10).

Another protein TSSK found to have kinase activity is necessary for male fertility as they are localised in the spermatids which is HSP90 dependent. It was found that this kinase associates with HSP90 as it results in reduced expression after incubation with HSP90 inhibitors and kinases. TSSK-1,2,4,6 phosphorylates H2A histone where as TSSK3 doesn't show any kinase activity. TSSK-1,2,6 reduced in expression when treated with HSP90 inhibitors indicating that HSP90 is required for their maintenance of half life and also catalytic activity of TSSK-4,6. TSSK 2 and 6 undergoes ubiquitination directly when inhibited with inhibitors of HSP90 and undergoes proteosomal degradation but without change in their mRNA levels (23).

Ion channels and transporters as male fertility factors

Another protein catsper localised in sperm tail is necessary for sperm motility, calcium influx and fertilisation in mice. Catsper 1 was found to be one of the four important proteins of calcium channels necessary for male fertility in mice (24) and also in humans. In case of sperm motility ca2+ influx is necessary for hyper activation in males and in female genital tract the ca2+ influx is necessary for capacitating and high motility penetration of sperm in to oocytes.

Slc26A8 is a testis anion transporter expressed in sperm and necessary for sperm motility and required for fertilisation potential in males. It is an anion transporter and doesn't involve in the maturation of gonads of mice. Slc26A8 is found to be localised in the annulus that connects the midpeice to principal piece of the flagella. It was shown that the ability of consumption of ATP was reduced due to defects in mitochondrial sheath even though the motor protein expression in flagella is normal and was found that null mutation of the protein leads to compromise in normal maturation of sperm and capacitation in the mice and humans (25).

Is oxidative stress preventing enzymes and structural maintenance proteins are necessary for sperm function:

Superoxide dismutase, catalase and glutathione peroxidise plays an important role in relation to oxidative stress. SOD level changes was associated with changes in sperm count where as catalase with sperm morphology and GPx expression levels was found to be not associated with any of the sperm parameters (26).

There is no contributional research of nuclear matrix proteins in relation to sperm parameters up to now. So, study of proteins of nuclear matrix sperm was found to be useful. Proteins identified in the sperm head include mostly chaperons, cytoskelet al. proteins, peroxiredoxins, isomerases and other enzymes (27).

Other proteins involved in male fertility

Amyloid precursor protein is normally known for its activity in alzeihmers disease but its role in male fertility was not known. This protein was first identified in testis and studied for its interaction with testis. It is now known to interact with RANB9 protein and 37 proteins in which COPS5 has highest correlation coefficient where as CD81 and CD 99 with C= 0.029 and 0.064 respectively (28).

GPr56 is an adhesion protein necessary for male fertility. It was found to be expressed in testis cords, PM cells, localised in Sertoli cells and germ cells but found to be absent in interstitial cells. GPr56 is highly expressed in sertoli cells and spermatogonial cells with reduced expression in PM cells. Production of progeny with defective testis is seen with GPr56 null mice as the spermatic cords are disrupted and scattered instead of forming tubular structures. There is also basement membrane disruption in the testis with no alterations in FSH, LH and testosterone probably showing no effect on these harmones (29).

TEX 101, a testicular germ cell specific protein is found to be located in the plasma membrane of germ cells. It does not affect the mating but secreted as one of the GPI anchored proteins by TACE in to the seminal fluid. However the mechanism of action of protein was not clearly understood (30).

DEFB114 is the β-defensin highly expressed in the caput and corpus regions of epididymis. It shares cysteine conserved regions and cysteine pairing regions (Cys10–Cys24, Cys3–Cys31, Cys14–Cys32) with β-defensin members. It is involved in maintenance of male fertility through preserving sperm motility in LPS challenged mice by neutralising it in a dose dependent manner (31).

Rbm5 is the pre – mRNA splicing factor present in the nucleus and cytoplasm of spermatocytes and round spermatids. R263 was found to be the highly conserved region in the Rbm5 and loss of function allele mutation leads to arrest of pups' production as it is necessary for RNA binding in the RNA recognition motif and change in β- strand structure necessary for the binding of protein. This mutation doesn't effects the fertility in females. The protein is necessary for sperm differentiation and the mutation leads to in azoospermia due to arrest at stage 8 of haploid sperm development which is independent on hormones FSH, LH and testosterone. The loss of function in this protein leads to testis atropy as it is highly expressed in testis compared to other tissues (32).

St5, is involved in MAP Kinase pathway which is necessary for the cell growth, post testicular maturation and fertilisation and necessary to be explained in detail. The splicing by Rnm5 produce 61 transcripts in which 126 Kda fragment was involved in regulating the MAP kinase pathway and found to contain high amounts of p-ERK1/2 than ERK1/2 . Regulation in sperm differentiation by protein in wild type than mutant indicates its regulation in tumor growth (33).

Nanos 2 is the protein encoded by the gene Nanos that acts as translational repressor in germ cells and expressed in the cytoplasm of germ cells of seminiferous tubules of testis during prenatal period. The molecular weight of protein was found to be more than 15Kda. It is highly expressed in the peri tubular cells and its localisation is different during prenatal and adult stage. H68Q and H109H are the mutations localised in the zinc finger domain commonly found in Nanos 2. It form complexes with the proteins like (DAZ and BOL, PUMILIO2, NANOS1, respectively) but its role in male fertility is not clearly understood (33).

Table 1 Proteins role in male fertility, localisation and functions other than male fertility and their chromosomal distribution

Name of the protein	localisation	Role in male fertility	Functions other than male fertility	organism	Chromosomal distribution	Reference
Protein phosphatase 4 (PP4)	-	Meiotic chromosome dynamics	Dephosphorylation events during cell cycle and DNA damage response	Universal regulator	6	Aya Sato-Carlton et al. (2014).
Catsper	Principal piece	Sperm motility	Not known	Mice, humans	11	Md Saidur Rahman et al. (2017) Jean-Ju Chung et al. (2017)
Superoxide dismutase(SOD), catalase	Seminal plasma	Sperm count (SOD) Sperm morphology (catalase)	Free radical scavengers	universal	6 (MnSOD) 11 (catalase) in humans	Borgstahl GE et al. *(1992)* NG_013339.1 RefSeqGene
Amyloid precursor protein (APP)	Tail and head region	Sperm motility and sperm-oocyte interaction	Receptor like and adhesive properties in nervous system	ubiquitously	21	Joana Vieira Silva et al. (2015) Brooks WS et al. (1995)
SSTK (ser/thr kinase)	Heads of elongated spermatids	chromatin condensation, reconstruction of the sperm cytoplasm, acrosome formation, and development of the flagellar apparatus.	Associates with HSP 90 and HSP70	Rat, dog, mouse, human, cow	19	Nikolay A. Spiridonov et al. (2005)
GPR56 an adhesion G-protein coupled receptors	Sertoli cells	Development of male gonads	Inhibition of melanoma progression, brain function	mammals	16	Guangchun Chen et al. (2010)
TEX101	Plasma membrane of germ cells	Spermiogenesis and fertilization	Binds to uPA/uPAR complex and mediates the effects	mice	19	Christina G. Schiza et al. (2014)
B- defensin 114	Epididymis and saliva, gingival keratinocytes	Protection against LPS loss of fertility	Anti inflammative	humans	6p 21	Heguo Yu et al. (2013)
Testis anion transporter Slc26a8	Spermatocytes and spermatids	Germ cell function and differentiation.	Transport sulphate in a chloride dependent manner	bacteria, yeast, plants, nematodes and mammals	9p24.2	Everett, L.A et al. (1999) Mount, D.B et al. (2004),
RBM5	Spermatogonia, round spermatids and spermatocytes	pre-mRNA splicing regulator in round spermatids	Apoptosis, lung histology	Humans and mouse	9	Moira K. O'Bryan et al. (2013)
Nanos2	germ cells.	translational repressor necessary for germ-cell development	Meiosis suppression	Widely spread	19	K.M. Kusz et al. (2009). uniprot
DYNLT1	head, tail and mid piece	Spermatogonial cell division and differentiation	Protein trafficking, membrane vesiculation, cell cycle regulation, and stem cell differentiation.	Mouse	4 and 17	Sivankutty Indu et al. (2015), NCBI

DYNLT1 is a gene that found associated with t-complex of testis. It is localised in sperm head, mid piece and sperm tail and in infertile men. The localisation was restricted to head and mid piece only. It is known to cause male sterility in loss of function and restoration of the fertility with BAC construct of the protein in mice, fly and humans. Its molecular weight was found to be 14Kda. It is a component of microtubular network and over expression of HSP 90 along with DYNLT1 leads to phosphorylation of Thr 94 which plays a role in cell division. DYNLT1 is found to be involved in sperm division and differentiation (34).

DISCUSSION

Proteins plays a key role in the biological systems as enzymes, transcription factors, antibodies, cytokines etc., so, instead of focusing

on the sperm morphology, and sperm parameters concentrating on molecules involved in maintaining genome integrity proves to be helpful in understanding their role in male fertility. Some of the proteins are ion channels maintaining ca2+ influx during motility and capacitation. Some of them are useful for DNA compaction as they are involved in phosphorylation of histones in sperm. Absence of some proteins leads to loss of fertility as they are responsible for sperm division and differentiation like DYNLT1 and found to be involved in cargo binding, lymphocyte division, vesicular transport and human embryo implantation.

Most of the proteins which are discussed here are responsible for sperm motility and male fertility but not focussed in the female. Amyloid precursor protein in patients with alziehmers disease should be studied for interactions related to fertility. Some of the proteins acts as antioxidants preventing oxidative stress also play a role in sperm count and morphology where as defensin DEFB114 found to preserve fertility in lipopolysaccharide mice which seems its involvement in immune reactions may be as pattern recognition molecule.

Some of the proteins like Rbm5 are known to interact with other proteins and involved in prevention of continous cell division in germ cells and also acts as splicing factor of pre mRNAs of apoptotic proteins such as caspase, FAS receptor and C- FLIP. It indicates its control on cell division preventing the tumorigenic growth in tissues apart from male fertility.

REFERENCES

1. Mosquera, L. Forristall, C. Zhou, Y. King, ML. (1993) A mRNA localized to the veget al. cortex of Xenopus oocytes encodes a protein with ananos-like zinc finger domain. Development; 117:377–386.
2. Kobayashi, T. Miyazaki, T. Natori, M. and Nozawa, S. (1991). “Protective role of superoxide dismutase in human sperm motility: superoxide dismutase activity and lipid peroxide in human seminal plasma and spermatozoa,” Human Reproduction, vol. 6, no. 7, pp. 987–991.
3. Pilon, M. Weisblat, DA. (1997). A nanos homolog in leech. Development; 124:1771–1780
4. Subramaniam, K. Seydoux, G. (1999). nos-1 and nos-2, two genes related to Drosophila nanos, regulate primordial germ cell development and survival in Caenorhabditis elegans. Development; 126: 4861–4871.
5. Mochizuki, K. Sano, H. Kobayashi, S. (2000). Nishimiya-Fujisawa C, Fujisawa T. Expression and evolutionary conservation of nanos-related genes in Hydra. Dev Genes Evol;210:591–602
6. Koprunner, M. Thisse, C. Thisse, B. Raz, E. (2001). A zebrafish nanos-related gene is essential for the development of primordial germ cells. Genes Dev; 15:2877–2885
7. Tsuda, M. Sasaoka, Y. Kiso, M. Abe, K. Haraguchi, S. Kobayashi, S. Saga, Y. (2003). Conserved role of nanos proteins in germ cell development. Science; 301:1239–1241.
8. Haraguchi, S. Tsuda, M. Kitajima, S. Sasaoka, Y. Nomura-Kitabayashid, A. Kurokawa, K. Saga, Y. (2003). nanos1: a mouse nanos gene expressed in the central nervous system is dispensable for normal development. Mech Dev; 120:721–731.
9. Aya Sato-Carlton, Xuan Li, Oliver Crawley, Sarah Testori, Enrique Martinez-Perez, Asako Sugimoto, Peter Carlton, M. (2014). Protein Phosphatase 4 Promotes Chromosome Pairing and Synapsis, and Contributes to Maintaining Crossover Competence with Increasing Age PLOS Genetics, Volume 10, Issue 10, e1004638.
10. Nikolay Spiridonov, A. Lily Wong, Patricia Zerfas, M. Matthew Starost, F. Svetlana Pack, D. Cloud Paweletz, P. and Gibbes Johnson R. (2005). Identification and Characterization of SSTK, a Serine/Threonine Protein Kinase Essential for Male Fertility. Molecular and cellular biology, p. 4250–4261.
11. Mount, D.B. and Romero, M.F. (2004) The SLC26 gene family of multifunctional anion exchangers. Pflugers Arch., 447, 710–721.
12. Kobayashi, S. Yamada, M. Asaoka, M. Kitamura, T. (1996). Essential role of the posterior morphogen nanos for germline development in Drosophila. Nature; 380:708–711.
13. Padron, O. F. Lynne, C.M. Brackett, N. L. Thomas Jr ,A. J. Sharma, R. K. and Agarwal, A. (1997). “Seminal reactive oxygen species and sperm motility and morphology in men with spinal cord injury,” Fertility and Sterility, vol. 67, no. 6, pp. 1115–1120.
14. Ollero, M. Gil-Guzman, E. Lopez, M. C. et al., (2001). “Characterization of subsets of human spermatozoa at different stages of maturation: implications in the diagnosis and treatment of male infertility,” Human Reproduction, vol. 16, no. 9, pp. 1912–1921.
15. Fujii, J. Iuchi, Y. Matsuki, S. and Ishii T. (2003), “Cooperative function of antioxidant and redox systems against oxidative stress in male reproductive tissues,” Asian Journal of Andrology, vol. 5, no. 3, pp. 231–242.
16. Yona, S. Lin, HH. Siu, WO. Gordon, S. Stacey, M. (2008). Adhesion-GPCRs: emerging roles for novel receptors.Trends Biochem Sci.; 33:491–500. [PubMed: 18789697]
17. Harrison, A. Olds-Clarke, P. and King, S. M. (1998) Identification of the t complex-encoded cytoplasmic dynein light chain tctex1 in inner arm I1 supports the involvement of flagellar dyneins in meiotic drive. J. Cell Biol. 140, 1137–1147
18. King, S. M. Dillman, J. F. III, Benashski, S. E. Lye, R. J. Patel-King, R. S.and Pfister, K. (1996) The mouse t-complex-encoded protein Tctex-1 is a light chain of brain cytoplasmic dynein. J. Biol. Chem. 271, 32281–32287
19. Campbell, K. S. Cooper, S. Dessing, M. Yates, S. and Buder, A. (1998) Interaction of p59fyn kinase with the dynein light chain, Tctex-1, and colocalization during cytokinesis. J. Immunol. 161, 1728–1737
20. O’Neill, M. J. and Artzt, K. (1995) Identification of a germ-cell-specific transcriptional repressor in the promoter of Tctex-1. Development 121, 561–568
21. Tai, A. W. Chuang, J. Z. and Sung, C. H. (1998) Localization of Tctex-1, a cytoplasmic dynein light chain, to the Golgi apparatus and evidence for dynein complex heterogeneity. J. Biol. Chem. 273, 19639–19649
22. Dedesma, C. Chuang, J. Z. Alfinito, P. D. and Sung, C. H. (2006) Dynein light chain Tctex-1 identifies neural progenitors in adult brain. J. Comp Neurol. 496, 773–786
23. Kula Jha, N. Alyssa Coleman, R. Lily Wong, Ana M. Salicioni, Elizabeth Howcroft , and Gibbes Johnson, R. (2013). Heat Shock Protein 90 Functions to Stabilize and Activate the Testis-specific Serine/Threonine Kinases, a Family of Kinases Essential for Male fertility, The journal of biological chemistry vol. 288, no. 23, pp. 16308–16320
24. Matthew R. Avenarius Michael, S. Hildebrand, Yuzhou Zhang, Nicole, C. Meyer,Luke. L.H. Smith, Kimia Kahrizi, Hossein Najmabadi,and Richard Smith J.H.(2009). The American Journal of Human Genetics 84, 505–510.
25. Aminata Toure, Pierre Lhuillier, Jan A. Gossen, Cor W. Kuil, David Lho te, Bernard Je´gou, Denise Escalier and Ge´rard Gacon (2007). Human Molecular Genetics,, Vol. 16, No. 15 1783–1793.
26. Macanovic B, Vucetic M, Jankovic A, Stancic A, Buzadzic B, Garalejic E, Korac A, Korac B, and OtasevicV (2015). Hindawi Publishing Corporation Disease Markers, Article ID 436236, 5 pages http://dx.doi.org/10.1155/2015/436236
27. Kichine E, Falco MD, Barbara F. Hales, Robaire B, Chan P (2013) Analysis of the Sperm Head Protein Profiles in Fertile Men: Consistency across Time in the Levels of Expression of Heat Shock Proteins and Peroxiredoxins., PLOS ONE, Volume 8, Issue 10, e77471.
28. Silva JV, Yoon S, Domingues S, Guimarães S, Alexander V Goltsev, Silva EFC, José Fernando F Mendes, Odete Abreu Beirão da Cruz e Silva and Fardilha M (2015). Amyloid precursor protein interaction

network in human testis: sentinel proteins for male reproduction BMC Bioinformatics, 16:12, DOI 10.1186/s12859-014-0432-9.
29. Chen G, Yang L, Begum S, and Xu L. (2010). GPR56 Is Essential for Testis Development and Male Fertility in Mice; Dev Dyn. Author manuscript; available in PMC 239(12): 3358–3367. doi:10.1002/dvdy.22468.
30. Schiza C, G. Keith Jarvi, Diamandis E, .and Andrei Drabovich P. (2014).An emerging role of TEX101 protein as a male infertility biomarker eJIFCC Vol25No1pp009-026
31. Dong HJ, Liu, Aijie XinYH, Shi H, Sun F, Zhang Y, Lin D, and Diao. H (2013). The Novel Human -Defensin 114 Regulates Lipopolysaccharide (LPS) -mediated Inflammation and Protects Sperm from Motility Loss. The journal of biological chemistry VOL. 288, NO. 17, pp. 12270–12282.
32. Moira O'Bryan, K. Brett Clark, J. Eileen McLaughlin, A. Rebecca D'Sylva, J. Liza O'Donnell, Jacqueline, A. Wilce Sutherland, J. Anne O'Connor, E. Belinda Whittle, Christopher Goodnow, C. Christopher Ormandy, J. Duangporn Jamsai. (2013). RBM5 Is a Male Germ Cell Splicing Factor and Is Required for Spermatid Differentiation and Male Fertility. PLOS Genetics, Volume 9, Issue 7, e1003628.
33. Kusz, K.M. Tomczyk, L. Sajek, M. Spik, A. Latos-Bielenska, A. Jedrzejczak, P. Pawelczyk, L. and Jaruzelska, J. (2009).The highly conserved NANOS2 protein: testis-specific expression and significance for the human male reproduction Molecular Human Reproduction, Vol.15, No.3 pp. 165–171.
34. Sivankutty, Indu. Sreeja, C. Sekhar. Jeeva, Sengottaiyan. Anil Kumar, Sathy M. Pillai. Malini, Laloraya. and Pradeep G. Kumar. (2015).Aberrant Expression of Dynein light chain 1 (DYNLT1) is Associated with Human Male Factor Infertility, Molecular & Cellular Proteomics Vol 14, issue12, 3185-95.
35. Md Saidur Rahman, Woo-Sung Kwon, Myung-Geol Pang (2017). Prediction of male fertility using capacitation-associated proteins in spermatozoa. Mol Reprod Dev.84:749 –759
36. Jean-Ju Chung, Kiyoshi Miki, Doory Kim, Sang-Hee Shim, Huanan F Shi, Jae Yeon Hwang, Xinjiang Cai, Yusuf Iseri, Xiaowei Zhuang, and David E Clapham (2017). CatSperζ regulates the structural continuity of sperm Ca^{2+} signaling domains and is required for normal fertility. eLife. 2017; 6: e23082
37. Borgstahl GE1, Parge HE, Hickey MJ, Beyer WF Jr, Hallewell RA, Tainer JA.(1992).The structure of human mitochondrial manganese superoxide dismutase reveals a novel tetrameric interface of two 4-helix bundles. Cell. 1992 Oct 2;71 (1): 107-18 .
38. Brooks WS, Martins RN, De Voecht J, Nicholson GA, Schofield PR, Kwok JB, Fisher C, Yeung LU, Van Broeckhoven C. (1995). A mutation in codon 717 of the amyloid precursor protein gene in an Australian family with Alzheimer's disease. Neurosci Lett. 1995 Oct 27;199(3):183-6.
39. Heguo Yu, Jing Dong, Yihua Gu, Haiyan Liu, Aijie Xin, Huijuan Shi, Fei Sun, Yonglian Zhang, Donghai Lin and Hua Diao (2013). The Novel Human β-Defensin 114 Regulates Lipopolysaccharide (LPS)-mediated Inflammation and Protects Sperm from Motility Loss. J Biol Chem. 2013 Apr 26; 288(17): 12270–12282.
40. Everett, L.A., and Green, E.D. (1999). A family of mammalian anion transporters and their involvement in human genetic diseases. Hum. Mol. Genet. 8, 1883–1891.

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